

High-dose chemotherapy with autologous stem-cell transplantation for relapsed metastatic germ cell tumors

The Alberta experience

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ABSTRACT

INTRODUCTION: High-dose chemotherapy with autologous stem-cell transplantation (HDC-ASCT) is standard therapy for metastatic germ cell tumors (mGCTs) in patients whose disease progresses during or after conventional chemotherapy. We conducted a retrospective review of HDC-ASCT in relapsed mGCT patients in the province of Alberta, Canada, over the past two decades.

METHODS: Patients with mGCTs who received HDC-ASCT at two provincial cancer referral centers from 2000–2018 were identified from institutional databases. Baseline clinical and treatment characteristics were collected, as well as overall survival (OS) and disease-free survival (DFS). Relevant prognostic variables were analyzed.

RESULTS: Forty-three patients were identified. The median age was 28 years (range 19–56). A majority (95%) had non-seminoma histology and testis/retroperitoneal primary (84%). Twenty patients (47%) had poor-risk disease, as per The International Germ Cell Consensus Classification (IGCCC), at start of first-line chemotherapy. HDC-ASCT was used as second-line therapy in 65% of patients, and 58% of ASCT patients received tandem transplants. Median followup after ASCT was 22 months (range 2–181). At last followup, 42% of patients were alive without disease, including 3/7 (43%) of patients with primary mediastinal disease. Two-year and five-year DFS/OS ratios were 44%/65% and 38%/45%, respectively. Median OS and DFS for all patients were 30.0 months (13.3–46.6) and 8.0 months (0.9–15.1), respectively.

CONCLUSIONS: We found that HDC-ASCT is an effective salvage therapy in mGCT, consistent with existing literature. Patients appeared to benefit regardless of primary site. Although limited by small sample size, we found a numerical difference in DFS and OS between second- and third-line HDC-ASCT and single vs. tandem ASCT.

INTRODUCTION

Germ cell tumors (GCTs) represent the most common malignancy affecting men aged under 40 years, and account for the greatest average number of years of life loss of any adolescent or adult malignancy.^{1,2} The majority of patients with metastatic GCT (mGCTs) are cured with initial cisplatin-based chemotherapy with prognosis based on the International Germ Cell Consensus Classification (IGCCC);³ however, patients with recurrent or progressive mGCTs after first-line chemotherapy have a poor prognosis despite further treatment, with two-year disease-free survival (DFS) ranging from 6–75%, depending on clinical risk factors.⁴

Conventional-dose chemotherapy (CDC) or high-dose chemotherapy with autologous stem-cell transplantation (HDC-ASCT) are both used as salvage treatment options for patients with relapsed mGCT after first-line treatment. CDC regimens, such as ifosfamide, cisplatin and vinblastine (VelP), etoposide (VIP), or paclitaxel (TIP), have been studied in single-arm trials, with long-term remission rates of 23–63%.^{5,6} Based on a single-institution study from Indiana University, HDC-ASCT was studied in 184 patients with relapsed mGCT treated with 1–2 cycles of high-dose carboplatin and etoposide followed by ASCT. At a median followup of 48 months, 63% achieved a durable remission with five-year overall survival (OS) of 65%.⁷

A more recent retrospective analysis from the Indiana University

KEY MESSAGES

- Our retrospective quality assurance chart review confirmed that HDC-ASCT is an effective salvage therapy in the treatment of metastatic GCTs.
- Our findings indicate that patients with mGCTs can benefit from HDC-ASCT regardless of primary tumor site.
- Tandem HDC-ASCT treatments may result in higher OS and DFS rates compared to single HDC-ASCT, although larger patient sample sizes are required to reach firm conclusions.

reported two-year progression-free survival (PFS) of 63% for 303 patients who received HDC-ASCT as second-line therapy and two-year PFS of 49% for 61 patients who received HDC-ASCT as third-line or later therapy.⁸

An international, multicenter series reported survival outcomes of 1594 patients with relapsed mGCT treated with either carboplatin-based HDC-ASCT or CDC, with two-year PFS of 50% vs. 28%, and five-year OS of 53% vs. 41%, favoring HDC-ASCT. The benefit was consistent across all prognostic groups, except low-risk patients. Adverse prognostic factors include extragonadal/mediastinal GCT, poor response to initial cisplatin-based chemotherapy, levels of alpha fetoprotein (AFP; $\mu\text{g/L}$) and human chorionic gonadotropin (HCG; IU/L) >1000 at relapse, and presence liver/bone/brain metastases.⁹

To date, the only published randomized control trial comparing CDC to HDC-ASCT failed to show superiority of HDC-ASCT, although this study was limited by its methodology (outdated treatment protocols).¹⁰ Moreover, although there was a sizeable patient population, a significant proportion of patients randomized to HDC-ASCT did not receive this treatment.¹⁰ As such, the optimal salvage treatment strategy has not yet been well-elucidated. Other unanswered questions related to HDC-ASCT include the optimal number of cycles required, predictive/prognostic factors for efficacy, and timing of HDC-ASCT.

Alberta is a geographically diverse Canadian province with a population of approximately four million people. HDC-ASCT in Alberta is performed at two regional oncology referral centers: The Cross Cancer

Institute (CCI) in Edmonton and the Tom Baker Cancer Center (TBCC) in Calgary. We sought to examine the outcomes of mGCT patients undergoing HDC-ASCT in Alberta, as well as examine treatment patterns that may influence these outcomes.

METHODS

Male patients aged ≥ 18 years old who received HDC-ASCT for mGCT of testicular, retroperitoneal, or mediastinal primary at CCI and TBCC from January 1, 2000, to December 31, 2018, were identified from prospective databases maintained at both centers. Both paper charts and electronic medical records were used to collect relevant patient data. DFS was defined as the first day of HDC to disease progression or death. OS was defined as the first day of HDC to death or censored at the time of last followup. Survival outcomes were analyzed using the Kaplan-Meier method and Cox's proportional hazard model. Prognostic variables were analyzed initially using univariate analysis and variables significant at $p < 0.10$ were entered in the multivariable analysis. The final predictive model was chosen based on a p -value < 0.05 . Due to low patient numbers, i.e., patient sample sizes, multivariate analysis was not significantly powered and thus unstable. Hence, the final predictive model used to assess survival outcomes was univariate regression analysis. Data was processed in IBM SPSS Statistics Version 25.0 (IBM Corp., Armonk, NY, U.S.).

RESULTS

Adult patients who received HDC-ASCT for relapsed mGCT at Alberta cancer referral centers between 2000 and 2018 were identified. Seven patients did not meet eligibility criteria and were excluded from this study: one patient with a primary tumor of unknown origin; two patients with primary central nervous system GCTs; three female patients; and one patient who received HDC-ASCT as a first-line therapy. Figure 1 diagrams the selection criteria for the current study in CONSORT format.

Twenty-three patients (53.5%) were treated with HDC-ASCT at the CCI in Edmonton, while 20 patients (46.5%) were treated at the TBCC in Calgary. The median patient age was 28 years (range 19–56). At the start of HDC-ASCT, most patients had non-seminoma histology (95.3%, $n=41$), while six patients (4.6%) had seminoma. Likewise, most patients had either testicular or retroperitoneal primary tumors (83.7%, $n=36$), with seven patients (16.3%) having mediastinal primary tumors. Twenty patients had an IGCCC risk status

of poor (46.5%) at HDC-ASCT initiation, while 16 patients had an IGCCC status of intermediate (37.2%), and seven had a risk status of good (16.3%). Twenty-nine patients had platinum-sensitive disease and 14 had platinum-refractory disease, defined as progression within four weeks after the most recent cisplatin-based chemotherapy. Details of baseline patient demographics and clinical characteristics at HDC-ASCT introduction are listed in Table 1.

Most of the 43 patients either received, or were scheduled to receive, tandem HDC-ASCT treatment (Table 2). Ultimately, 18 patients (41.8%) received single HDC-ASCT, while 25 patients (58.2%) received tandem HDC-ASCT. Ten patients (23.3% of total study patients) were originally intended to receive single HDC-ASCT, all occurring in 2007 and prior. An additional eight patients were originally planned to receive tandem therapy, but ultimately received single HDC-ASCT. These eight patients did not receive a second cycle of HDC-ASCT due to two patients refusing, two toxicity events, two with insufficient stem cell collection, and two cases of progressive disease after the first HDC-ASCT treatment, each representing 5.6% of the 43 total study patients. Of the 43 patients studied, 28 (65.1%) received HDC-ASCT as a second-line treatment, while 15 patients (34.9%) received it as a third- or fourth-line treatment.

Median followup from HDC-ASCT initiation was 22 months (range 3–181); the median followup for surviving patients was 60.5 months (range 12–181). The Kaplan-Meier median DFS estimate for all patients was eight months (Figure 2), with an observed DFS range of 0.9–15.1 months. Two-year and five-year DFS rates were 44% and 38%, respectively. When codified by treatment characteristics, two-year DFS rates were 50% for second-line HDC-ASCT, and 33% for third-line or later therapy. Similarly, second-line HDC-ASCT had a five-year DFS of 45%, compared to a lower DFS of 25% when used as third-line or later salvage therapy.

When categorized by primary tumor site, patients with mediastinal disease had a two-year DFS of 57% and a five-year DFS of 43%, while patients with testicular or retroperitoneal primary tumors had two-year and five-year DFS rates of 41% and 38%, respectively. At last followup, 42% of patients (18/43) were alive and disease-free, including the three patients who presented with poor prognosis primary mediastinal disease.

The OS estimate for all patients was 30.0 months (range 13.1–46.6) (Figure 3). Patient two-year and five-year OS rates were 65% and 45%, respectively. Two-year OS was 71% in patients who received second-line

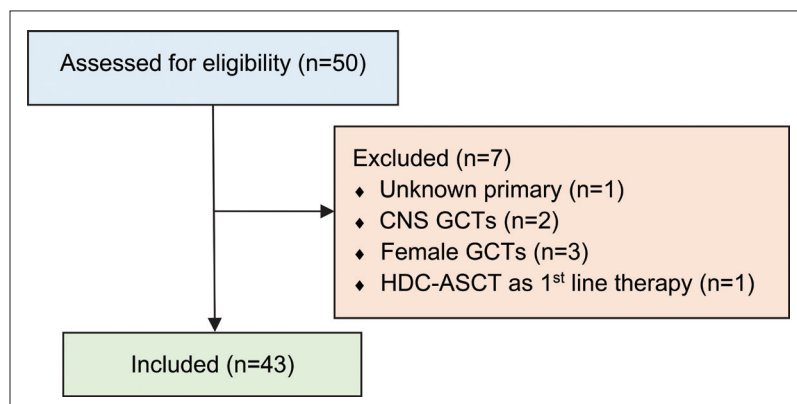


Figure 1. CONSORT diagram. Selection criteria from the current retrospective review. CNS: central nervous system; GCT: germ cell tumor; HDC-ASCT: high-dose chemotherapy with autologous stem-cell transplantation.

HDC-ASCT treatment, and 53% in those patients who received third-line or later line therapy. At five years, OS was 56% for patients receiving second-line HDC-ASCT therapy vs. 23% for those receiving HDC-ASCT in the third- or fourth-line setting.

Patients with primary mediastinal disease showed OS of 71% at two years post-therapy initiation, and an OS rate of 54% at five years. Patients with primary testicular or retroperitoneal tumors had two-year and five-year OS rates of 64% and 43%, respectively. The two-year DFS/OS ratio was 44%/65% for all patients, while at five years, the DFS/OS decreased to 38%/45%, respectively.

Analysis of patient survival outcomes based on intention to treat (ITT) of single HDC-ASCT vs. tandem therapy reveals these subsets to have IIT-comparative OS rates of 40% and 63% at two years post-therapy initiation, and OS rates of 40% and 48% at five years, respectively. Similarly, ITT DFS rates for tandem vs. single therapy were 45% and 40% at two years, and 41% and 40% at five years post-therapy initiation, respectively. Statistical analysis by the Cox proportional hazards model reveals a hazard rate ratio (HR) for OS between tandem vs. single HDC-ASCT of 0.72 (95% confidence interval [CI] 0.28–1.84, $p=0.493$), and a tandem vs. single HR for DFS of 0.70 (95% CI 0.28–1.75, $p=0.445$). Two- and five-year patient survival outcomes relative to treatment and disease classifications are detailed in Table 3.

Univariate analyses were performed to assess the individual effects of disease or treatment variables on the predictive values of patient DFS and OS in the absence of all other covariates. Univariate Cox regression as the hazard model for the effects of third-line vs. second-line ASCT, site of primary tumor, or tandem vs. single stem cell transplantation on patient five-year DFS

Demographic	n	%
Median age (range)	28	19–56*
Site of HDC-ASCT		
Edmonton	23	53.5%
Calgary	20	46.5%
Histological type		
Seminoma	2	4.7%
Non-seminoma/mixed	41	95.3%
Site of primary		
Testis or retroperitoneal	36	83.7%
Mediastinal	7	16.3%
Risk status at first-line chemotherapy (IGCCC)		
Good	7	16.3%
Intermediate	16	37.2%
Poor	20	46.5%
Response to first-line chemotherapy		
Complete response	6	14.0%
Partial response	37	86.0%
Platinum sensitivity**		
Sensitive	29	67.4%
Refractory	14	32.6%
hCG level pre-ASCT		
≥1000 IU/L	6	14.0%
≤1000 IU/L	37	86.0%
αFP level pre-ASCT		
≥1000 µg/L	2	4.7%
≤1000 µg/L	41	95.3%
Beyer Lorch score†		
0–1	16	37.2%
2	7	16.3%
3	8	18.6%
4	7	16.3%
5–6	5	11.6%

*Range. **Most recent cisplatin therapy. †IGCCC-2 prior to HDC-ASCT. αFP: alpha-fetoprotein; hCG: human chorionic gonadotropin; HDC-ASCT: high-dose chemotherapy with autologous stem-cell transplantation; IGCCC: International Germ Cell Consensus Classification.

Characteristic	n	%
Number of cycles of HDC-ASCT received		
Single	18	41.8%
Tandem	25	58.2%
Line of therapy when HDC-ASCT used		
2	28	65.1%
3	13	30.2%
4	2	4.7%
Reasons for not using tandem transplant		
Planned single	10	55.6%
Patient refusal	2	11.1%
Toxicity	2	11.1%
Insufficient collection	2	11.1%
Progression after 1st transplant	2	11.1%
HDC regimens		
Carboplatin + etoposide	16	37.2%
Carboplatin + etoposide + cyclophosphamide	21	48.8%
Carboplatin + etoposide + ifosfomide	4	9.3%
Carboplatin + thiotepa + cyclophosphamide	2	4.7%
Post-HDC-ASCT therapy		
None	19	44.2%
Salvage surgery	9	20.9%
Palliative chemotherapy	10	23.3%
Palliative radiotherapy	7	16.3%
Radical radiotherapy	2	4.7%
Pathology from salvage surgery		
Scar	3	7.0%
Teratoma	2	4.7%
Active germ cell	3	7.0%
Not available	1	2.3%

HDC-ASCT: high-dose chemotherapy with autologous stem-cell transplantation.

and OS are presented in Figures 4a and 4b. None of these variables presented significantly different HR for DFS or OS from analysis of our study cohort; however, second-line ASCT showed a trend towards improved five-year OS rates over third-line ASCT, with a HR of 2.1. Multivariate analysis was uninformative (data not

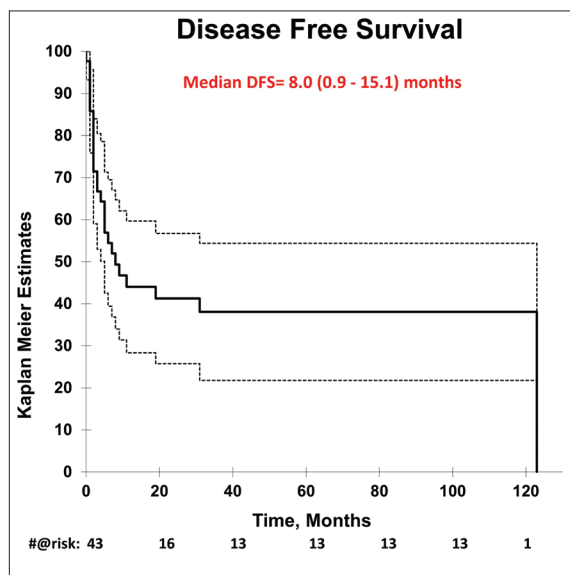


Figure 2. Kaplan-Meier estimates of disease-free survival (DFS). Hatched lines denote 95% confidence interval (CI).

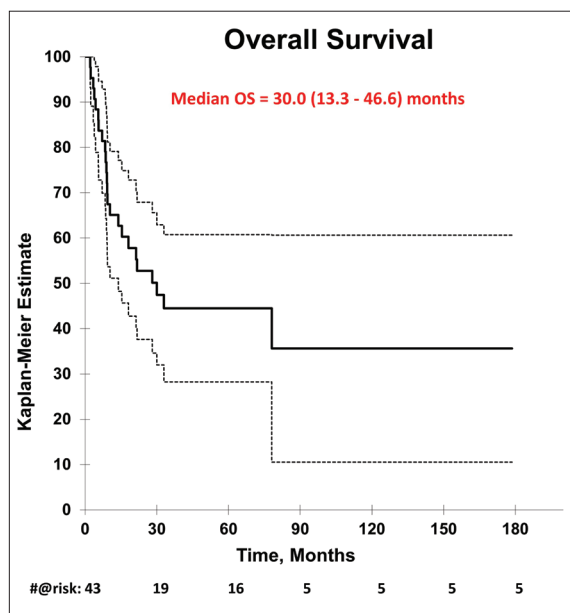


Figure 3. Kaplan-Meier estimates of overall survival (OS). Hatched lines denote 95% confidence interval (CI).

Classification	DFS (%)		OS (%)	
	2-year	5-year	2-year	5-year
All patients	44	38	65	45
2nd-line HDC-ASCT	50	45	71	56
3rd-line or later HDC-ASCT	33	25	53	23
Single (n=10)	40	40	40	40
Tandem (n=33)	45	41	63	48
Mediastinal primary	57	43	71	54
Testis/retroperitoneal primary	41	38	64	43

DFS: disease-free survival; HDC-ASCT: high-dose chemotherapy with autologous stem-cell transplantation; OS: overall survival.

management of patients with recurrent or progressive disease after first-line therapy remains a challenge. The prognosis for these patients is poor, and no optimal treatment strategy has been identified. Options include CDC regimens, including cisplatin, ifosfamide with either paclitaxel (TIP), etoposide (VIP), or vinblastine (VeIP), or HDC-ASCT.^{6,7,12}

Despite these treatment advances, prospective evidence supporting the superiority of one salvage strategy over another is lacking. The TIGER randomized study (*ClinicalTrials.gov* identifier: NCT02375204), which compares CDT to HDC-ASCT using modern treatment regimens of four cycles of TIP vs. 1–2 cycles of ifosfamide and paclitaxel followed by three cycles of high-dose carboplatin and etoposide, is ongoing. The results of the TIGER study will provide needed clarity on optimal salvage strategies.

Regardless of a particular regimen, several retrospective and prospective studies have demonstrated that HDC-ASCT is an effective salvage therapy, with a significant proportion of patients achieving long-term DFS.^{7-10,13-15}

Our study has revealed several important observations. Notably, most patients were planned to receive tandem (58%) as opposed to single HDC-ASCT, and no single HDC-ASCT regimens were planned after 2007. In addition, tandem compared to single HDC-ASCT treatments demonstrated higher OS and DFS rates, although these outcome differences were not statistically significant. Larger patient numbers would have been required to reach firm conclusions on differential outcomes from these data. Nevertheless, a large, multicenter, retrospective study involving 2395 HDC-

shown) and so univariate regression analysis was the predictive model assessing survival outcomes.

DISCUSSION

The introduction of cisplatin-based chemotherapy regimens has revolutionized the management of mGCTs, with more than 80% of patients expected to be cured after first-line chemotherapy.¹¹ Despite this success, the

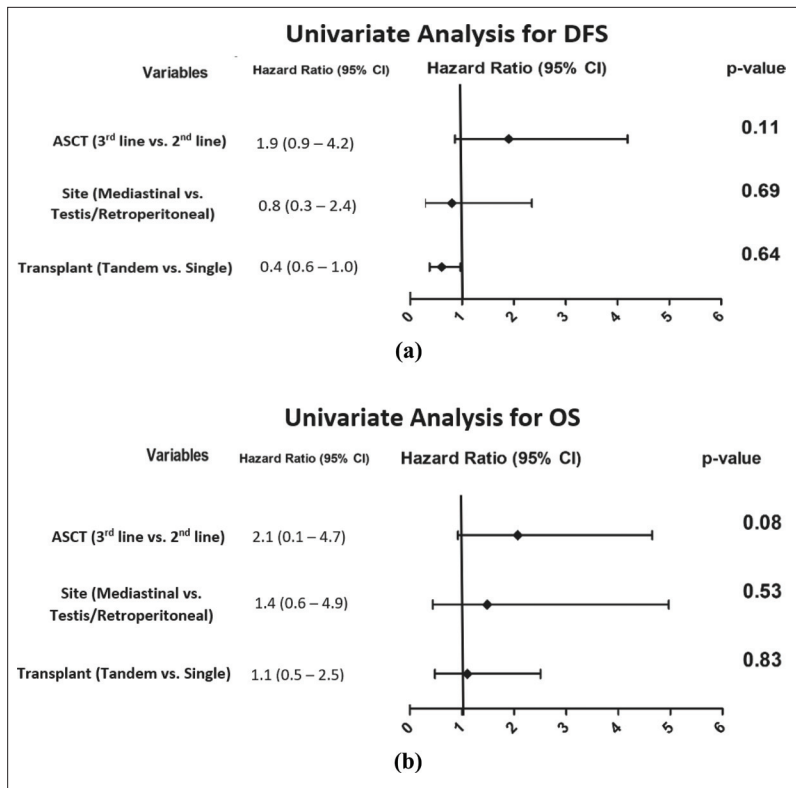


Figure 4. (a) Forest plot illustrating results of univariate analysis of prognostic variables on patient 5-year disease-free survival rates (DFS). (b) Forest plot illustrating results of univariate analysis of prognostic variables on patient 5-year overall survival (OS) rates. ASCT: autologous stem-cell transplantation; CI: confidence interval.

ASCT recipients found a tandem approach resulted in superior PFS and OS compared to single treatment.¹³ To our knowledge, the only study that compared single vs. multiple HDC-ASCT cycles in a randomized, prospective fashion reported similar five-year PFS for both arms, but also fewer treatment-related deaths in the tandem arm, resulting in higher OS.¹⁴

Our study has demonstrated that most patients (76%) who were planned to receive tandem HDC-ASCT were able to receive it. Elsewhere, the disparity between planned and received tandem HDC-ASCT has been variably reported as low as 47% to as high as 94%.^{8,14,15} This variability is undoubtedly due to differences in time, patient populations, and treatment regimens used. Approximately two-thirds of the patients in our study received HDC-ASCT as their second-line or first salvage therapy. While the choice of first salvage treatment is controversial and must take into consideration patient factors and preferences, the use of HDC-ASCT appears to achieve superior outcomes as first-line salvage therapy when compared to second- or later-line of salvage.^{8,13}

Finally, long-term survival can be achieved even in patients with a very poor prognosis, such as those

with mediastinal primaries. In our series, 3/7 patients achieved five-year DFS after HDC-ASCT, similar to that of gonadal and retroperitoneal primaries. Other reported series have also demonstrated long-term DFS in this and other high-risk populations, such as those with platinum-refractory disease.⁸ Consequently, the use of HDC-ASCT should be considered for the treatment of mGCTs even in those patients at highest risk.

Strengths and limitations

Because Alberta has a single-payer, publicly funded, universal healthcare system that provides all oncology services, the data captured in this study are representative of the outcomes achieved in this population as a whole. Therefore, our data is qualitatively different from data reported by other centers, which can have bias based on geographic and socioeconomic referral patterns

Nonetheless, the study is not without limitations. Its small size and retrospective nature limit the conclusions that can be made when comparing differences in patient and treatment variables. In larger studies, the site of primary tumor, pre-treatment tumor markers, and platinum-sensitivity appear to be significant predictors of disease progression and survival. Future prospective studies are warranted to help identify patients who may be cured from CDC without the need for HDC-ASCT, given the potential toxicities. Our study did not specifically evaluate the short-term and long-term toxicities of HDC-ASCT. Nevertheless, this review provides important validation of the effectiveness of the use of HDC-ASCT as salvage therapy in male patients in Alberta with relapsed/progressive advanced GCTs.

CONCLUSIONS

Our study demonstrates the outcomes of HDC-ASCT performed at the two regional referral centers in Alberta over approximately the last two decades. Reassuringly, this study has demonstrated similar outcomes to those reported by other groups, demonstrating favorable survival outcomes in a contemporary patient population and treatment approach and adding evidence to the benefit of this treatment in a poor-prognosis patient population. This study also confirms that outcomes achieved in the province of Alberta, Canada, are similar to other centers, providing necessary quality assurance.

COMPETING INTERESTS: Dr. Zhang has participated in advisory board for Novartis AAA, and Pfizer. Dr. Alimohamed has had advisory/consultancy roles with AstraZeneca, Bayer, BMS, EMD Serono, Gilead, Merck, Pfizer, and Seagen. Dr. Basappa has been an advisory board member for AstraZeneca, Bayer, BMS, Eisai, EMD Serono, Ipsen, Janssen, Merck, Pfizer, Roche, and

Seagen; and has received travel support from Eisai and Janssen. Dr. Heng has been an advisory board member for Bayer, BMS, Eisai, Exilexis, Ipsen, KGA, Merck, Novartis, and Pfizer. Dr. North has received honoraria from AAA, Astellas, BMS, EMD Serono, Janssen, Merck, and Roche. Dr. Kolinsky has received honoraria from Astellas, AstraZeneca, Bayer, BMS, Eisai, EMD Serono, Ipsen, Janssen, and Merck; and has participated in clinical trials supported by Astellas, AstraZeneca, Bayer, BMS, Eisai, EMD Serono, Ipsen, Janssen, Merck, and Seattle Genetics. The remaining authors do not report any competing personal or financial interests related to this work.

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REFERENCES

1. Average years of life lost per person dying of cancer, all races, both sexes, 2004. SEER DATABASE 1975–2004. NIH. Published 2004. Available at: http://seer.cancer.gov/csr/1975_2004/results_figure/sect_01_zfig_19.pdf. Accessed Nov. 20, 2023.
2. Chung P, Warde P. Testicular cancer: Germ cell tumors. *BMJ Clin Evid* 2016;2016. <https://doi.org/10.1016/B978-0-323-24098-7.00055-1>
3. International germ cell consensus classification: A prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. *J Clin Oncol Off J Am Soc Clin Oncol* 1997;15:594-603. <https://doi.org/10.1200/JCO.1997.15.2.594>
4. Lorch A, Beyer J, Bascoul-Mollevi C, et al. Prognostic factors in patients with metastatic germ cell tumors who experienced treatment failure with cisplatin-based first-line chemotherapy. *J Clin Oncol Off J Am Soc Clin Oncol* 2010;28:4906-11. <https://doi.org/10.1200/JCO.2009.26.8128>
5. Daugaard G. Management of poor-prognosis or relapsed germ-cell cancer. *BJU Int* 2009;104:1392-7. <https://doi.org/10.1111/j.1464-410X.2009.08865.x>
6. Kondagunta GV, Bacik J, Donadio A, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. *J Clin Oncol Off J Am Soc Clin Oncol* 2005;23:6549-55. <https://doi.org/10.1200/JCO.2005.19.638>
7. Einhorn LH, Williams SD, Chomness A, et al. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. *N Engl J Med* 2007;357:340-8. <https://doi.org/10.1056/NEJMoa067749>
8. Adra N, Abonour R, Althouse SK, et al. High-dose chemotherapy and autologous peripheral-blood stem-cell transplantation for relapsed metastatic germ cell tumors: The Indiana University experience. *J Clin Oncol Off J Am Soc Clin Oncol* 2017;35:1096-102. <https://doi.org/10.1200/JCO.2016.69.5395>
9. Lorch A, Bascoul-Mollevi C, Kramar A, et al. Conventional-dose vs. high-dose chemotherapy as first salvage treatment in male patients with metastatic germ cell tumors: Evidence from a large international database. *J Clin Oncol Off J Am Soc Clin Oncol* 2011;29:2178-84. <https://doi.org/10.1200/JCO.2010.32.6678>
10. Pico JL, Rosti G, Kramar A, et al. A randomized trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumors. *Ann Oncol Off J Eur Soc Med Oncol* 2005;16:1152-9. <https://doi.org/10.1093/annonc/mdt228>
11. Ko JJ, Bernard B, Tran B, et al. Conditional survival of patients with metastatic testicular germ cell tumors treated with first-line curative therapy. *J Clin Oncol Off J Am Soc Clin Oncol* 2016;34:714-20. <https://doi.org/10.1200/JCO.2015.64.7909>
12. Loehrer PJS, Lauer R, Roth BJ, et al. Salvage therapy in recurrent germ cell cancer: Ifosfamide and cisplatin plus either vinblastine or etoposide. *Ann Intern Med* 1988;109:540-6. <https://doi.org/10.7326/0003-4819-109-7-540>
13. Kilari D, D'Souza A, Fraser R, et al. Autologous hematopoietic stem cell transplantation for male germ cell tumors: Improved outcomes over 3 decades. *J Am Soc Blood Marrow Transplant*. 2019;25:1099-106. <https://doi.org/10.1016/j.bbmt.2019.02.015>
14. Lorch A, Kleinhans A, Kramar A, et al. Sequential versus single high-dose chemotherapy in patients with relapsed or refractory germ cell tumors: Long-term results of a prospective randomized trial. *J Clin Oncol Off J Am Soc Clin Oncol* 2012;30:800-5. <https://doi.org/10.1200/JCO.2011.38.6391>
15. Hamid AA, Markt SC, Vicier C, et al. Autologous stem-cell transplantation outcomes for relapsed metastatic germ-cell tumors in the modern era. *Clin Genitourin Cancer* 2019;17:58-64.e1. <https://doi.org/10.1016/j.clgc.2018.09.009>

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